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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,506	02/28/2002	Dennis A. Holt	327E USC2	3727

7590 02/04/2004

ARIAD Gene Therapeutics, Inc.
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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,506	HOLT ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 2 are pending in the application.

Priority

1. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Also, the **current status of all nonprovisional parent applications referenced should be included**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for examples 23-30 for the monomers and 31-67, 77 and 78 for the multimerizing agent, does not reasonably provide enablement for all of the compounds embraced by the genus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO MAKE: The nature of the invention in the instant case has claims which embrace a wide range of chemically and physically distinct compounds, wherein M^1 and M^2 in claim 1 and M^B and $M^{B'}$ in claim 2 are a substituted piperidine or pyrrolidine and macrocyclic rings thereof; and L can be a variety of functional linking groups, including heterocyclic rings. The scope of the compounds of claims 1 and 2 reads on a plethora of aliphatic, heteroaliphatic, aryl and heteroaryl substituents (R^1, R^2 and R^3), a linker moiety (L), and macrocycylic structures where R^1 and R^2 are joined together. The exact nature of these substituents are vague and indefinite in that it is not clear exactly how large the substituent may be; the position of the heteroatoms in the heteroaliphatic moiety; the size, position or point of attachment of the aryl and heteroaryl moieties; etc. While several specific multimerizing agents or monomers are disclosed, there is insufficient guidance for preparing additional multimerizing agents or monomers which would be effective in the following utilities: e.g. to activate the transcription of a desired gene, actuate apoptosis, or trigger other biological events in engineered cells growing in culture or in whole organisms, including in gene therapy applications.

There are several preferred embodiments disclosed herein. One preferred embodiment of the instant invention is multimerizing agents or monomers, which have a IC50 value in the Competitive Binding FP Assay better than 1000 nM, e.g. human FKBP12. Another preferred embodiment of the compounds is where those, which are capable of inducing a detectable signal in a 2-hybrid transcription assay based on fusion proteins containing FKBP domain. Preferably, the FKBP domain is an FKBP domain other than wild-type human FKBP12". Another preferred embodiment of the compounds is where those, which are capable of inducing a detectable signal in such an FKBP-based apoptosis assay. Preferably, the FKBP domain is an FKBP domain other than wild-type human FKBP12".

Testing is provided for only a few of the claimed compounds at the page between pages 82-87 of the specification. Examples should be of sufficient scope as to justify the scope of the claims. However, the generic claims are much broader in scope than is represented by the testing. Note the broad definitions for R^1, R^2 and R^3 in the generic claims, which are defined as aliphatic, heteroaliphatic, aryl or heteroaryl and L which is a linker moiety. These definitions embrace many structurally divergent groups not represented in the testing. Markush claims must be provided with support in the disclosure. Markush claims are subject to rejection based upon the lack of supporting disclosure when the working examples fail to include written description(s) which teach how to make and use Markush members embraced thereby in full, clear, and exact terms. See In re Fouche 169 USPQ 429. The compounds tested are not seen as adequately representative of the compounds encompassed by the extensive Markush groups instantly claimed for the uses instantly asserted and claimed.

This area of activity can be expected to be highly structure specific and unpredictable, as is generally true for chemically-based pharmacological activity. In view of the structural divergence in the claims, one skilled in the art could not reasonable extrapolate the activities of some of the claimed compounds to the other structurally divergent compounds embraced by the claims which have not been tested. In view of the breadth of the claims, the unpredictability in this area of activity, and the limited amount of guidance and examples in the specification, one skilled in the art would have to undergo an undue amount of experimentation to prepare the claimed compounds.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

3. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claim 1 is vague and indefinite in that the terminology a multimerizing agent does not clarify whether the claim is limited to a compound, composition, or even complex composition.

b) Claim 1 is vague and indefinite in that it is not known what is meant by "nd" in the 6th line of page 88.

c) Regarding claim 1, the phrase "i.e." renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

See MPEP § 2173.05(d). See the definition of Y in line 13 of page 88 and the definition of R^1 and R^2 in line 1 of page 89.

d) Claim 2 is vague and indefinite in that it is not known what is meant by C1-C10 aliphatic. It is believed that the applicants intended C_1-C_{10} aliphatic.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by WO 96/06097. WO 96/06097 teaches the compounds of the instant invention where Y is a covalent bond; X is O; R^1 is 1,3-diphenylpropyl $-C(CH_3)_2-CH_2-CH_3$; R^2 of M^1 to R^2 of M^2 through L is $-C(CH_3)_2-CH_2-O-C(=O)-NH-CH_2-$(1,4-phenylene)$-CH_2-NH-C(=O)-O-CH_2-C(CH_3)_2-$ as shown in example 78, R^2 of M^1 to R^2 of M^2 through L is $-C(CH_3)_2-CH_2-O-C(=O)-NH-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-NH-C(=O)-O-CH_2-C(CH_3)_2-$ as shown in example 77, or R^2 is $-C(CH_3)_2-CH_2-CH_3$ and R^1 of M^1 to R^1 of M^2 through L is -CH(CH_2CH_2-Ar)-(1,3-phenylene)$-O-CH_2-C(=O)-NH-CH_2-$(1,4-phenylene)$-CH_2-NH-C(=O)-CH_2-O-$(1,3-phenylene)-CH(CH_2-CH_2-Ar)- as shown in example 40, etc.

It is recognized benefit of U.S. Serial Number 09/690,797 filed October 17, 2000 as well as 08/808,276 filed February 28, 1997 which is a CIP or provisional applications 60/033,035 filed December 10, 1996, 60/024,861 filed August 28, 1996, and 60/012,432

filed February 28, 1996 and 08/793,016 filed August 18, 1995 and 08/479,694 filed June 7, 1995 which is a CIP of 08/292,598 filed August 18, 1994 is being urged. However, the applicant's priority documents do not describe the invention of this application serial number 10/086,506. Note for benefit under 35 USC 120 and 35 USC 119, there must be clear support (description and enablement) for claims instantly rejected herein as was set forth in In re Scheiber 199 USPQ 782; In re Lukach, 169 USPQ 795; In re Gostelli, 10 USPQ 2nd 1614; Kawai v. Metlesics 178 USPQ 159.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by SPENCER et al., Science. SPENCER teaches the compounds of the instant invention where Y is a covalent bond; X is O; R^1 and R^2 are joined together forming a macrocyclic structure; and L is $-CH_2-CH_2-O-C(=O)-NH-CH_2-$(1,4-phenylene)$-CH_2-NH-C(=O)-O-CH_2-CH_2-$, $-NH-CH_2-(CH_2)_8-CH_2-NH-$, $-NH-CH_2-$(1,4-phenylene)$-C(=O)-NH-CH_2-(CH_2)_8-CH_2-NH-C(=O)-$(1,4-phenylene)$-CH_2-NH-$, $-NH-CH_2-$(1,4-phenylene)$-CH_2-NH-$, etc. as shown in the examples on page 1019.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by UCHIYAMA et al., Peptide Chemistry. UCHIYAMA teaches the compounds of the instant invention where Y is O; X is NH; R^2 is Me and the R^1 of M^1 and R^1 of M^2 is bound through L. See Reg No. 158222-02-7.

7. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by BOGER et al., Journal of the American Chemical Society. BOGER teaches the compounds of the instant invention where X is NH; W is NH; R^1 and B^2 of both moieties are joined

together through a linker or bound through L. See Reg No. 151961-29-4; 151961-30-7; 151961-28-3; 100940-65-6; etc.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by FAILLI et al., U.S. Patent No. 5,162,333. FAILLI teaches the compounds of the instant invention where Y is a covalent bond; X is O; R^1 and R^2 are joined together forming a macrocyclic structure as shown in the examples 1 and 2.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by KAO et al., U.S. Patent No. 5,120,727. KAO teaches the compounds of the instant invention where Y is a covalent bond; X is O; R^1 and R^2 are joined together forming a macrocyclic structure as shown in the examples 1-5.

10. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by BOCK et al., U.S. Patent No. 5,225,528. BOCK teaches the compounds of the instant invention where W is NH; X is O or NH; R^1 is benzyl and/or B^3 of one or both moieties (i.e. M^B or $M^{B'}$) is joined together through L or a linker to R^1 of the other moiety. See Reg No. 138775-46-9; 138773-51-0; 138773-57-6; 138773-58-7; 138773-59-8; 138773-61-2; 138773-62-3; 138773-63-4; 138773-64-5; 138773-65-6; 138773-74-7; 138774-03-5; 138774-04-6; 138797-64-5; etc.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/06097. The generic structure of WO 96/06097 encompasses the instantly claimed compounds (see Formula II, page 1) as claimed herein. Examples 78, 77, 40, etc. differ only in the nature of the n, X, Y, R^1 and R^2 substituents. Page 1, line 32 through page 2, line 21 defines the substituent n is 1 or 2, X is O, NH or CH_2, Y is O, NH, NR^3 or represents a direct bond, R^1, R^2 and R^3 are independently C_1-C_{20} alkyl or aryl. Compounds of the instant invention are generically embraced by WO 96/06097 in view of the interchange ability of n, X, Y, R^1 and R^2 substituents of the monomers. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example n = 1 as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

12. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over FAILLI et al., U.S. Patent No. 5,162,333. The generic structure of FAILLI encompasses the instantly claimed compounds (see the structure in column 2, line 1) as claimed herein. Examples 1 and 2 differ only in the nature of the instant n, X, Y, R^1 and R^2 substituents. Column 2, lines 1-56 defines the corresponding instant substituents where n is 2, X is O, Y is a direct bond, R^1, R^2 and R^3 are such that M^1 and M^2 form macrocyclic monomers bound together through instant L. Compounds of the instant invention are generically embraced by FAILLI in view of the interchange ability of the instant R^1, R^2 and R^3 substituents of the monomers. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example where R^1 of FAILLI is substituted with a carboxy group as well as other possibilities from the

generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

13. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over KAO et al., U.S. Patent No. 5,120,727. The generic structure of KAO encompasses the instantly claimed compounds (see the structure in column 2, line 1) as claimed herein. Examples 1-5 differ only in the nature of the instant n, X, Y, R^1 and R^2 substituents. Column 2, lines 1-60 defines the corresponding instant substituents where n is 2, X is O, Y is a direct bond, R^1, R^2 and R^3 are such that M^1 and M^2 form macrocyclic monomers bound together through instant L. Compounds of the instant invention are generically embraced by KAO in view of the interchange ability of the instant R^1, R^2 and R^3 substituents of the monomers. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example where A of KAO is $-CH_2$-(1,4-phenylene)-CH_2- as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

14. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over BOCK et al., U.S. Patent No. 5,225,528. The generic structure of BOCK encompasses the instantly claimed compounds (see Formula I, column 2) as claimed herein. The examples differ only in the nature of the instant n, X, Y, R^1, B^1, B^2 and B^3 substituents. Column 2, line 45 through column 6, line 26 defines the corresponding instant substituents where n is 1 or 2, X is O or NH, W is NH, R^1, B^1, B^2 and B^3 are such that M^B and $M^{B'}$ form a macrocyclic monomers bound together through instant L and a linker. Compounds of the instant invention are generically embraced by BOCK in view of the interchange ability of the instant R^1, B^1, B^2 and B^3 substituents of the monomers.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example where R^1 of BOCK is substituted with an imidazole moiety as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claim 2 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 4-8 of U.S. Patent No. 6,133,456. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of the instant invention encompass the compounds of U.S. Patent No. 6,133,456.

16. Claim 2 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 and 47-51 of U.S. Patent No. 6,150,527. Although the conflicting claims are not identical, they are not patentably

distinct from each other because the compounds of the instant invention encompass the compounds of U.S. Patent No. 6,150,527.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 703-305-1880. The examiner can normally be reached on 8:30-5:00 Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting -SPE of 1624 at 571-272-0661.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda Coleman
Primary Examiner Art Unit 1624
February 2, 2004